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BY

DAVID ALEXANDER SHIRRES, M.D.,
Professor of Neurology, University of Vermont; Neurologist, Montreal General Hospital; Lecturer in Pathology, McGill University, Montreal.

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REGENERATION OF THE AXONES OF SPINAL NEURONES IN MAN.

BY

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Professor of Neurology, University of Vermont; Neurologist Montreal General Hospital; Lecturer in Pathology, McGill University, Montreal.

Gentlemen,—The subject I have to discuss to-day is regeneration of the axones of the spinal neurones in man. I shall deal with the results of personal observation to a large extent and have considered it expedient to make but few references to the extensive literature bearing upon the subject.

Considerable doubt as to the possibility of regeneration taking place, is widely expressed. Numerous experimenters have operated upon monkeys, dogs and other animals; but so far as I am aware—except in the recent paper by Dr. James Collier in *Brain*, where he states that immediate suture experiments upon the spinal cords of animals have shown that regeneration is possible—have failed to establish the fact that regeneration takes place in the spinal axones.

Sir William Gowers, in his text book on Diseases of the Nervous System, Vol. 1., in discussing transverse myelitis of the cord refers to the possibility of regeneration taking place, and he notes a case where at one time a very considerable destruction of the cord was present with symptoms approaching transverse division, namely, complete motor paraplegia, grave sensory disturbances, increased reflexes, bladder and rectal retention, etc. After many months a fair return of motion and sensation took place, spasticity being a marked feature After the lapse of years the patient died from some intercurrent ailment. Pathological sections of the cord were obtained at the seat of the myelitis, and in the crossed pyramidal tracts and other areas of the cord were found a number of very minute axones in a situation where normally large nerve fibres are usually seen, and he was of the opinion that those smaller fibres were regenerated axones.

I do not know of any case in the literature in which transverse divis-

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Read before the Pan-American Congress at Panama, January, 1905.

ion of the cord in man was known to be complete, where regeneration has been demonstrated histologically and clinically, except in the case I shall discuss later, where complete transverse division of the cord was seen at the operation, and after the lapse of months clinical symptoms of regeneration were present with histological evidences at the post-mortem examination. There have been one or two cases reported as examples of total lesion with persistent knee jerks, but, that the lesion was absolutely complete, admits of doubt.

The supposed reason why regeneration does not take place in the spinal neurones of man, is the absence of the neurolemma sheath in those neurones. It has been established by many workers that the nuclei of the neurolemma sheath is a considerable factor in the regeneration of the peripheral nerves.

Being of the belief that regeneration could occur as shown by Gowers and others, I decided that upon the first opportunity, I should use every means in my power to aid such a case by appropriate treatment, and thereby help to produce regeneration.

In the large majority of cases injury of the cord takes place in the lumbar or lower dorsal segments. The time that would elapse before regeneration took place would be very considerable on account of the injury occurring in that part of the axones so remote from the cell bodies which are the seat of their vital functions. It is a well known fact that in suturing a divided peripheral nerve in the distal end of an extremity, considerably more time elapses before function is re-established than in those cases where the peripheral nerve has been sutured in the proximal part of the extremity, that going to show regeneration takes place quicker when the injury is in close proximity to the cell body.

Why is it, if regeneration does occur, as shown by Gowers, that so few cases improve after serious transverse myelitis, traumatic or otherwise, and that none, as far as I am aware, recovered where transverse division of the cord occurred due to fracture dislocation, and where at the operation complete severance of the cord was detected? Unfortunately many surgeons and neurologists, with serious results, frequently recommend, in cases of fracture dislocation of the spinal column associated with motor and sensory paralysis of the lower extremities, that operative procedure be delayed. In other cases where operation is advised at once the surgeon cuts down and removes the pressure on the cord and if transverse division is present, the prognosis being very serious, the patient is, as a rule, put back to bed and little more is done, with the result that grave secondary changes take place in the muscles, blood vessels and nerves and in that part of the cord below the seat of pressure or of transverse division. The extremities are allowed to fall by gravity into any position, and thereupon, stretching of certain muscles takes place, which hastens the onward progress of the condition. I have seen quite a number of cases and have read reports of others, where fracture dislocation had occurred and pressed upon the cord, producing motor and sensory paralysis, etc. Operation being performed at once, no damage to the structure could be detected macroscopically, yet the after results were very unsatisfactory.

The reason for this is as follows: If pressure be exerted upon the spinal cord suddenly, and it may be only momentarily, no changes may be detected in the structure by the eye, yet there is no doubt that a marked molecular change occurs in the axones of the spinal neurones inhibiting function,—as shown clinically by the paralysis of motion and sensation in the lower extremities, etc. In cases where the pressure is not momentary, but allowed to continue for a week or ten days and at the operation no alteration in the cord is detected, yet, like the above, the molecular change must be very grave and no doubt greater than the results where pressure is only momentary. Here not only molecular change may be present, but also local anæmia from pressure on the blood vessels, which if long continued will lead to necrotic changes.

The majority of cases of fracture dislocation and pressure on the cord, when brought into the hospital show the symptoms of motor and sensory paralysis with increased reflexes and spastic condition, pointing to a serious involvement of the cord, but not to transverse division, this last being indicated in those cases in which flaccid and sensory paralysis and loss of the reflexes is the symptom complex. An examination of the muscles of the lower extremities, if made at entrance usually show no alteration from normal to electrical stimulation. That is to say, when the lesion has been confined, as it is in the large majority of cases, to the lower dorsal cord, affecting only one or two segments, the lumbar enlargement is free from hæmatomyelia or any such injury as would produce an immediate effect on the lower motor neurone. After a day or so has elapsed in many of those cases, the reflexes are diminished and shortly after this reaction of degeneration becomes typical.

Now we see some cases may pass from a spastic to a flaccid state with abolition of the reflexes and reaction of degeneration, and, in a period varying from a few days to a week, present a typical picture of transverse division of the cord—motor and sensory paralysis, absence of the reflexes, flaccid state of the muscles and typical reaction of degeneration. If operation were carried out at this point, we should probably find on cutting down to the cord no alteration in structure macroscopically. Pressure being removed, the progress of the case is more frequently downwards than stationary. Why is this so? Pressure has produced molecular changes in the axones preventing stimulation from coming down or going up, with the result that we have isolation alteration or physiological deterioration, due to stimulation not being carried to the cells of the anterior horns below the lesion, with the result that changes such as flaccidity and reaction of degeneration in the muscles occur clinically, as above stated.

The cell bodies of the neurones to carry on their functions must have nourishment as well as stimulation, or they undergo degenerative changes or physiological alterations, and following this, secondary changes take place in the muscles and other structures of the extremities, as they, likewise, require stimulation and must be bathed in a healthy circulation. Now, stimulation and circulation cannot take place if the injury to the cord is as severe as above stated, and it is necessary that proper treatment such as electricity, massage and the prevention of deformity by the use of splints, and of adhesions of the joints by the frequent movement of the limbs should be carried out.

It has been shown by James Collier in cases of transverse division of the cord with a flaccid and sensory paralysis and loss of reflexes, that, by the use of electricity with needle electrodes placed into the muscles or nerves, after a time sufficient tone is produced in the muscles that upon striking the patella a reflex can be obtained. This goes to show very clearly the wonderful effect of electricity in producing tone, the presence of tone being an expression of an approach to normal condition of the structure acted upon.

The order of appearance of motor and sensory paralysis in progressive lesions is practically constant in the large majority of cases as follows: Motor paresis and spasticity, increase of the reflexes, anæsthesia below with local hyperæsthesia, sphincter paralysis, thermoanæsthesia and analgesia, tactile anæsthesia, followed by flaccidity with loss of the deep reflexes, progressive lowering of the faradic excitability, muscular wasting and loss of the sphincter tone. Pain and temperature are always earlier affected, and to a greater extent than sensibility to touch. The sensory loss in the usual cases, such as those involving the lower thoracic region involves the skin in order of the length of the sensory neurones supplying it, the soles of the feet being affected first, then the legs and later the thighs, but when the anæsthesia reaches the trunk it extends upwards in segmental order. When there is recovery the first signs to show themselves are, as a rule, subjective sensory disturbances. These are manifested in some cases first in the feet, while in others the distention of the bladder during the routine lavage is felt, or the patient becomes conscious of the act of micturition or catheterization. Next in order, slight tone makes its appearance, and this can be shown by tapping the muscle, which contracts. Later on the reflexes appear and become markedly increased and, associated with this, is a prominent spasticity, and faradic and galvanic excitability become normal. Sensibility then returns in the following order: Touch, pain, temperature, and usually the lowest sacral segments are sentient before the others. Voluntary power is last to return, the flexors being earlier affected than the extensors. Sometime after the patient has been able to walk the increased reflexes, spastic condition and Babinski sign are apparent, the latter being invariably the last of all to disappear.

Owing to the kindness of Dr. G. E. Armstrong, the following case came under my observation.

J. C., aged 48 years, a sailor, was brought into the Montreal General Hospital, under Dr. Armstrong's care in the spring of 1902, suffering from fracture dislocation of the spinal column in the region of the ninth and tenth dorsal vertebræ, with symptoms of flaccid paralysis, complete loss of motion and sensation and of the superficial and deep reflexes of the lower extremities and bladder and rectal retention. Twenty-four hours after admittance, Dr. Armstrong cut down over the seat of the fracture and removed the laminæ of the ninth and tenth dorsal vertebræ. Upon opening the dura mater a complete severance of the cord was found in this situation, with a gap of fully half an inch in extent between the two ends. On stimulating the anterior roots of the first and second lumbar segments with mild faradic current, with needle electrodes, the patient being only very slightly under the influence of the anæsthetic, contraction took place in the muscles of the leg. Stimulation was then applied to the posterior roots of the same segment and this was also followed by contraction of the muscles.

The above experiment was carried out for the following reasons: Considerable discussion had been going on as to the symptom complex present in cases of transverse division of the cord. Bastian, Brunn and others held the opinion that total transverse division of the cord was always followed by a flaccid paralysis, motor and sensory loss, with permanent abolition of the superficial and deep reflexes; others thought that while flaccid paralysis might occur at first, sooner or later a spastic condition set in. This second view was partly due to the influence of the opinions of many authorities who mistakenly compare the effects of transverse sections in dogs and in the higher apes with the sequence of events in man. Here also, physiologists frequently fail in impressing upon the mind of the student that the physiology of the nervous system in man and in the higher animals (and even in the higher apes) is not comparable. The student often sees the experiment carried out in those animals; they are printed upon his mind, and when at the bedside he is too apt to apply the physiology of the higher animals to man.

According to this second group of observers, if spasticity did not occur and flaccidity and loss of the reflexes still remained, not only in all probability had a transverse division of the cord occurred, but also a hæmatomyelia or some destructive lesion had taken place in the lumbar segment below the transverse lesion, and thereby injured the lower motor neurones, with the result that a flaccid paralysis was present.

Here in this case I was able to establish the fact that the segments below the division was in a more or less healthy condition, otherwise I could not have obtained a contraction of the muscles to faradic stimulation.

The separation of the cord having been found at the operation, as above stated, no hope of recovery was entertained, the patient was brought back to the ward and placed in bed.

This case, I thought, was a very suitable one to observe whether or not spasticity would develop, and I obtained permission from Dr. Armstrong to carefully observe the patient from time to time and carry out any method of treatment I could suggest. I held it advisable that an energetic and frequent application of faradic and galvanic stimulation be made to the extremities, so as to keep the muscles in as healthy a condition as possible. Fortunately, at this time I had a group of students who had taken a voluntary course in neurology extending over some six weeks, and with whom I had frequently discussed the ætiology of the reflexes and the symptom complex in spinal cord cases. Very little inducement was necessary to obtain relays of students to help me in treating the patient in the hope of arriving at some definite conclusion as to what symptoms are present in a case of this description, where, at the operation we had been able to demonstrate that the cord below the lesion was more or less healthy. Through their willingness I was able to obtain help and carry out treatment that I could not otherwise have done in a ward of a general hospital. Fortunately the patient was an interesting man. He was a sailor by occupation, had a retentive mind and related pleasing anecdotes about the different lands he had visited. He was of a genial disposition and had the ability of pleasing those who took part in his treatment. All the above factors, though seemingly unimportant, had a great deal to do with the results obtained in this case.

Weeks and months passed, but no return of the reflexes or alteration in the flaccid state of the limbs took place. By the treatment carried out, wonderful results were obtained, inasmuch as singularly few trophic or vaso-motor disturbances appeared in the extremities. Careful washing out of the bladder was attended to and everything was done to keep the patient in as perfect a condition as possible. No vestige of any sensory disturbances, subjective or objective, were at any time mentioned as occurring.

At the end of six months, no alteration taking place, I felt justified in holding to Bastian's opinion, that total transverse division of the cord is followed by permanent flaccid paralysis, sensory loss and abolition of the reflexes. At the operation the lower segment was found uninjured, since stimulation by the battery gave us positive contraction in the muscles. Here, then, by this means, for the first time on record, it was shown that the permanent loss of the knee jerk and the flaccid state are due to the removal of the higher centres, and not to any concomitant injury to, or consecutive structural change in, the lumbo-sacral segments.

Eleven months after the operation, and just about the time that the work of Purves Stuart and Ballance was brought out, stimulating our interest in the regeneration of the peripheral nerves, Dr. Armstrong wished to know whether I could suggest anything in the way of helping our patient. It had been shown that transplantation of the peripheral nerves could be successfully carried out and that even the intervention of foreign substances, such as catgut ligature or similar material placed between the ends of a divided nerve, would help to establish regeneration. Dr. Armstrong asked me whether I thought it would be of any use to transplant a dog's cord between the ends of the divided cord of our patient. My reply was that I did not know what would occur, but did not think any serious results were likely to follow and it might be worthy of a trial. He decided to have this operation carried out. A large dog was obtained, placed under chloroform, and an operation to expose the cord was carefully done under the most strict asepsis by two assistants, Dr. Barlow and Dr. Campbell. While this was being done our patient was put under chloroform and placed on the table. An incision was made over the seat of the old lesion, the dura mater opened and the cord exposed. At this time we found that a separation now existed between the two ends of the cord, about one and a half inch in extent. With a mild faradic current the anterior and posterior roots in the lower segment of the cord were stimulated, and a faint response took place in the muscles. The dog's cord to the extent of three inches was laid alongside the upper and lower segments of the patient's, a few fine stitches united the pia arachnoid of the one to the other, the dura mater was closed, the wound sutured, a plaster jacket applied and the patient taken back to the ward. He made a perfect recovery from the operation, the temperature on no occasion going over 100.

In the summer of 1903 I had the pleasure of informing Sir Victor Horsely of this operation having been carried out, and the results above mentioned, and he made the flattering remark that he thought Dr. Armstrong had achieved a great triumph in surgery in having carried out this operation without any septic results following; as one is well aware how difficult it is to operate on a dog with perfect aseptic technique.

A month passed without any apparent change. Fortunately I had another group of students who had attended my voluntary Christmas Vacation Course. I was able to instil in them an interest in the case, and was thereby able again to obtain help in giving the electricity and massage that I could not otherwise have done. The fifth week after the operation the patient was conscious of flatus in the lower quadrant of the abdomen. This he had never experienced before. Six days following this he became conscious of the passage of the catheter, when routine lavage of the bladder was being carried out, and ten days later he was able to inform the orderly that his bowels were about to move, and could tell when fæcal matter passed the rectum. On this date, for the first time, he complained of subjective sensations of pins and needles in the right foot, and a week later of the same symptoms in the left foot. Two months after the operation he described vividly and with all assurance subjective disturbances in both feet extending up to the knees. The passage of the catheter and the evacuation of the bowels were much more clearly felt.

At first we were inclined to think that this must be purely imagination, but when one heard the patient describe the condition with such exactitude, its coming and going, one began to think otherwise. Another reason for our coming to the belief that those feelings were real was that after the first operation the patient had as much care as after the second, and his desire and hope of recovery was just as keen if not more so than after the second, yet he never by any means gave the suggestion that such symptoms as above described were at any time present. Little alteration, progress or otherwise, from the above was noted until about the eighteenth day after the operation, when it was detected for the first time that with percussion of the pleximeter upon the muscles of the flexor aspect of the thigh and leg, the presence of a certain amount of tone was noticed by the contraction of the muscle. Neither at this time or at any time since the accident had voluntary movement or the return of objective sensory symptoms taken place. The reflexes, superficial and deep were still absent.

Sixteen days after this, for some unaccountable reason, the temperature ran up to 103°. The chest was normal and the bladder showed no symptoms of cystitis. The urine was carefully examined by the house surgeon, but nothing found pointing to any kidney trouble. From that day the patient began to lose his appetite and failed physically. Everything was done in the way of medicinal treatment, nourishing diet, etc., to keep up his general condition, but he slowly grew weaker and weaker, and finally died in the course of a fortnight. At the post mortem a large abscess was found in the right kidney, and this had been the probable cause of his death. Strange to say, as above mentioned, the urine was examined on two different occasions, after the onset of the fever, by the house doctor, but nothing pointing to any such disturbance was found.

The cord was carefully removed and placed in Muller fluid to harden. Six weeks later I opened up the dura mater and found lying between the two ends of the cord, where the injury had occurred, a diffluent mass. Sections of the cord above and below the lesion were put aside for Pal-Weigert stain, and the dura mater with its adherent mass between the ends of the cord was likewise prepared for Pal-Weigert stain. The sections of the upper segment revealed the typical ascending degenerations in the fields of Goll and Burdach, the direct cerebellar, and Gower's tracts. The sections below showed definite degenerations in the crossed and direct pyramidal tracts. The dura with its adherent substances which lay between the ends of the cord, after being stained by the Pal-Weigert method, showed a mass of minute myelin sheaths of nerve fibres which you may see by looking through the microscope placed before you. These fibres can be seen lying closely adherent to the dura mater and when traced upwards and downwards through the different sections, unite with the segments of the cord above and below, demonstrating the fact that regeneration of the axones of the spinal neurones had taken place, to a limited extent. Pal-Weigert stain, as you know, stains only the myelin sheaths. At the time of the operation the dura mater between the two segments was perfectly clear of nerve fibres to the naked eye.

I do not for a moment suggest that the dog's cord retained its vitality after it had been removed and placed inside the dural sheath, nor would I like to suggest that it was the dog's cord started the regeneration. I only want to speak here of the following facts, which you will see demonstrated under the microscope, that the nerve fibres are present and that they unite the two segments of the cord. Unfortunately, I did not place the cord in formalin or alcohol and, therefore, was unable to make a study of the lower segment by the Nissl method. From the sections you will see that this lower segment is comparatively speaking, in a fairly healthy condition. Sections through the cauda equina showed very little change, indeed, 90 per cent. of the nerve fibres making up this structure were to all intents and purposes normal by the Pal-Weigert stain.

I had the pleasure of showing the specimens at a meeting of the Lister Club at McGill University, where the pathologists without hesitation assented to the view that regeneration had taken place.

The success in this case, I think, was largely due to the patient having been so assiduously treated by electricity, the prevention of contractures and the frequent movement and massage of the extremities.

Since I have been connected with the Montreal General Hospital quite a few cases of pressure paralysis, without total lesion with motor and sensory paralysis, the result of fracture dislocation of the spinal column, have come under my care, where operation was carried out a very short time after the accident, yet satisfactory results were not obtained. In my opinion this was due largely in some of the cases to the fact that the massage, electricity, etc., were not applied.

In one case only, where I was fortunate in obtaining assistance in carrying out treatment, were good results obtained. This was of a patient of Dr. Kenneth Cameron's, who was brought into the hospital in the summer of 1903, suffering from pressure on the cord, the result of fracture dislocation, with complete flaccid paralysis, loss of the reflexes, grave sensory disturbances and bladder and rectal retention. At the operation Dr. Cameron found a fracture dislocation and displacement of the eleventh and twelfth dorsal laminæ with pressure on the cord, the result of the fracture, yet no macroscopical alteration in the structure was detected. The wound was closed up and the patient placed in a plaster jacket. More or less constant electrical treatment was carried out for six months. At the end of that time sensation had partially returned, and this was followed in a couple of months by the return of slight voluntary power. To-day, after a lapse of a year and a half, the patient comes regularly to my clinic for treatment, and is able to walk into the room without the aid of a stick.

The following is a case of Dr. Alexander Blackader's, which he kindly gave me permission to watch. I shall here relate only the essential facts denoting that a marked destructive lesion and probable hæmorrhage had occurred in the region of the fifth, sixth, seventh and eighth cervical segments of the cord on the right side, producing flaccid and atrophic paralysis of the right arm and spastic paralysis of the right leg with sensory symptoms of syringomyelia symptom complex, and the presence of enophthalmos in the right eye and exophthalmos in the left. For two months after entrance to the hospital the patient hung between life and death. At the end of that period he slowly recovered, and in seven months he left the hospital comparatively well. Since that time, two years have elapsed, and, during the interval, he has presented himself for examination, both at my office and at Dr. Blackader's. To-day he is as perfect a type of manhood physically as one could wish to see. He holds a position as locomotive engineer in the Grand Trunk Railway. The photograph, as you see, reveals an absolute symmetry in the muscles of all the extremities, going to show that regeneration of the neurones must have taken place in this case also.

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